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Diastereoselective formation of 2,3,4,5-tetrasubstituted tetrahydrofurans by a Lewis acid promoted addition of C3-substituted 1,3-bis(silyl)propenes to aldehydes

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ABSTRACT

A mild, efficient, Lewis acid promoted addition of C3-substituted 1,3-bis(silyl)propenes to aldehydes to provide the corresponding 2,3,4,5-tetrasubstituted tetrahydrofurans in excellent stereoselectivity is reported.

Substituted tetrahydrofurans are important structural motifs in organic chemistry and a feature in many biologically active natural products such as goniothalesdiol, 4-*epi*-larreatricin, and Ionomycin A (Fig. 1).[1] Thus, synthetic methods capable of targeting densely substituted tetrahydrofurans are of interest, and are required in order to synthesize and fully investigate the biological activity of this class of compounds. Many strategies toward such skeletons have been explored, however the majority of these methods concern the construction of di- and trisubstituted furans.[2] In contrast, only a few procedures for the synthesis of the more challenging tetrasubstituted tetrahydrofuran system have been described,[3] especially with regard to stereocontrol.

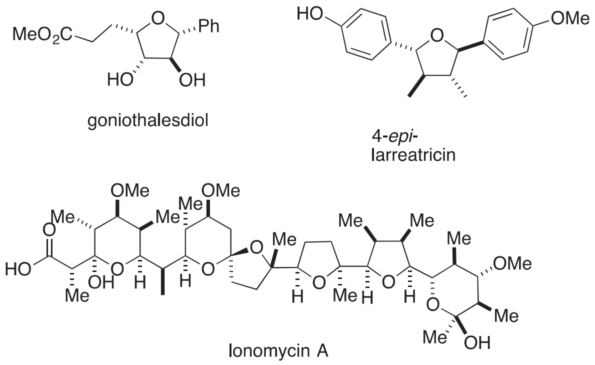

Figure 1. Some natural products containing tetrahydrofuran motifs.

We have previously shown that 1,3-bis(silyl)propenes are useful nucleophiles that can be used in [3+2] annulations with N-tosylated-α-amino aldehydes to yield pyrrolidines,[4] vinylation of glyoxylates and glyoxylamides,[5] and in the formation of (*E*)-1, 3-dienes.[6,7] In the present investigation, we have expanded the utility of the 1,3-bis(silyl)propenes in a mild, operationally straightforward procedure by which tetrasubstituted tetrahydrofurans can be obtained in a highly diastereoselective manner.

It has been shown that the addition of bissilane **2a** to aldehyde **1** affords diene **4a** in good yield and dr (80%, *E*/*Z* >98:2, Scheme 1).[6] In an attempt to expand this chemistry, silane **2b** was prepared and subjected to the optimized reaction conditions. To our surprise, however, this gave diene **4b** in only a modest yield [36%, (*E*, *E*) only] along with tetrahydrofuran **3b** (61%, single diastereomer). Encouraged by this result, it was decided to investigate the scope of the tetrahydrofuran formation, particularly if the selectivity for forming compound **3b** could be increased. The results of this study are outlined in Table 1.

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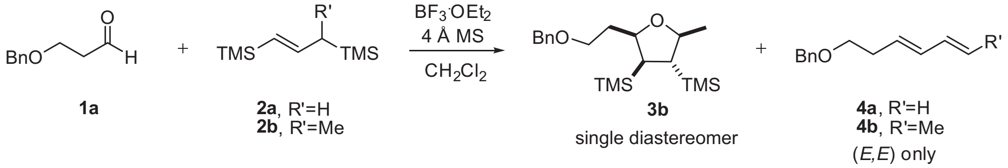
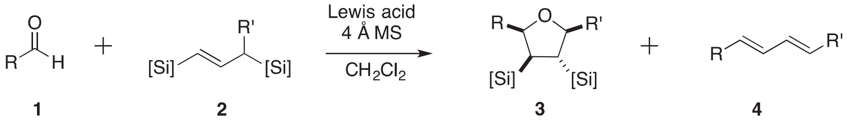


Scheme 1. Nucleophilic addition of 1,3-bis(silyl)propenes **2a**,**b** to aldehyde **1**.

Table 1 [a]



Entry	**1** (R)	**2**	[Si]	R′	Lewis acid	*T* (°C)	Product	Yield[b] (%) **3**	Ratio[c] **3**:**4**
1	**a**, $(CH_2)_2OBn$	**b**	TMS	Me	$BF_3\cdot OEt_2$	−78	**3b**	56[d]	61:39
2	**a**, $(CH_2)_2OBn$	**c**	Me_2PhSi	Me	$BF_3\cdot OEt_2$	−78	**3c**	0	—
3	**a**, $(CH_2)_2OBn$	**d**	Me_2BnSi	Me	$BF_3\cdot OEt_2$	−78	**3d**	0	—
4	**a**, $(CH_2)_2OBn$	**b**	TMS	Me	$MeAlCl_2$	−40	**3b**	27	83:17
5	**a**, $(CH_2)_2OBn$	**b**	TMS	Me	$TiCl_4$	−40	**3b**	—[e]	—
6	**a**, $(CH_2)_2OBn$	**b**	TMS	Me	$ScCl_3/NaSbF_6/TMSCl$	rt	**3b**	—[f]	—
7	**a**, $(CH_2)_2OBn$	**a**	TMS	H	$BF_3\cdot OEt_2$	−78	**3a**	0	0:1[g]
8	**a**, $(CH_2)_2OBn$	**b**	TMS	Me	$BF_3\cdot OEt_2$	−40	**3b**	86	86:14
9	**a**, $(CH_2)_2OBn$	**e**	TMS	*n*Pr	$BF_3\cdot OEt_2$	−78	**3e**	30	1:1
10	**a**, $(CH_2)_2OBn$	**e**	TMS	*n*Pr	$BF_3\cdot OEt_2$	−40	**3e**	67	67:33
11	**a**, $(CH_2)_2OBn$	**e**	TMS	*n*Pr	$BF_3\cdot OEt_2$	−20	**3e**	70	70:30
12	**a**, $(CH_2)_2OBn$	**f**	TMS	*i*Pr	$BF_3\cdot OEt_2$	−40	**3f**	>90	>90:10
13	**b**, COOEt	**b**	TMS	Me	$BF_3\cdot OEt_2$	−40	**3g**	—[f]	—
14	**c**, isatin	**b**	TMS	Me	$BF_3\cdot OEt_2$	−40	**3h**	—[f]	—
15	**d**, C_6H_{11}	**b**	TMS	Me	$BF_3\cdot OEt_2$	−40	**3i**	<10	55:45
16	**e**, $(CH_2)_2Ph$	**b**	TMS	Me	$BF_3\cdot OEt_2$	−40	**3j**	53	73:27
17	**e**, $(CH_2)_2Ph$	**b**	TMS	Me	$BF_3\cdot OEt_2$	−20	**3j**	49	70:30

[a] Reaction conditions: To a solution of **2**[8] (2 equiv) and the Lewis acid (2 equiv) in CH_2Cl_2 (1 mL) at −78 °C was added **1** (1 equiv, 0.01 M in CH_2Cl_2) dropwise over 1 h, and then the mixture was stirred for an additional 18 h.[9]

[b] Yield determined by ^1H NMR spectroscopy of the crude reaction mixture using 1-methylnaphthalene as an internal standard.

[c] The ratio of **3**:**4** was determined by ^1H NMR spectroscopy.

[d] Isolated yield.

[e] Decomposition of the starting material occured.

[f] No reaction.

[g] 95% Isolated yield of **4**.

Initial focus was directed toward investigating the reaction outcome when changing the steric and electronic properties of the silyl groups on **2**.[10] For example, by increasing the steric bulk of R′, it was hoped that the rate of the 1,3-Brook rearrangement of the adduct between aldehyde **1** and **2**,[11] which is a key step in the formation of diene **4**, could be reduced and thus favor the formation of tetrahydrofuran **3**.[12] However, the use of the more sterically hindered dimethylphenyl substituted bis(silyl)propene **2c** resulted in a poor conversion of aldehyde **1**, and neither tetrahydrofuran **3b** nor diene **4b** was formed (entry 2). Similarly, the application of dimethylbenzylsilyl derivative **2d** also gave low reactivity (entry 3). Next, the influence of different Lewis acids on the reaction outcome was studied (entries 4–6). The use of $MeAlCl_2$, which was previously proved to be the Lewis acid of choice in the [2+3] annulation reaction of N-tosylated-α-amino aldehydes,[13] resulted in low conversion, although higher selectivity in favor of the furan formation (entry 4). $TiCl_4$ yielded only decomposition of the starting material (entry 5), while the application of $ScCl_3/NaSbF_6/TMSCl$ gave no conversion (entry 6),[14] which might reflect the lower Lewis acidity of $ScCl_3$ compared to $BF_3\cdot OEt_2$[15] Next the impact of the C3-substituent on the bis(silyl)propene and the effect of the temperature, on the reaction outcome, were investigated in detail (entries 1, 7–12). When using bissilane **2a** (R′ = H) full consumption of the aldehyde was observed and the diene was the only product at −78 °C (entry 7), indicating that a substituent on the C3 position was necessary to provide additional stabilization to the intermediate carbenium ion. Accordingly, using bissilanes **2b** (R′ = Me) and **2f** (R′ = *i*Pr), the desired furans **3b** and **3f** were obtained, respectively (entries 8 and 12). It is interesting to note that bissilane **2e** (R′ = *n*Pr) reacted with lower selectivity compared to **2b** and **2f** (entry 10). A higher temperature resulted in increased yields and selectivities (compare entries 1 with 8, and 9 with 10 and 11) although the difference in going from −40 to −20 °C was not significant. With optimized reaction conditions in hand, the scope of this reaction was explored (entries 13–16). Both the addition of bis(silyl)propene **2b** to carboxylate **1b** and isatin **1c** proved to be unsuccessful (entries 13 and 14), while the addition of **2b** to cyclohexanal resulted in a low yield and selectivity (entry 15), the low conversion of the aldehyde probably being due to the increased steric hindrance in close proximity to the carbonyl moiety.

Hydrocinnamaldehyde **1e** was compatible with the reaction conditions providing **3j** in 53% and 19% yields (entries 16 and 17).

In conclusion, a novel method for the stereoselective formation of tetrasubstituted tetrahydrofurans under mild conditions has been developed.

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8. All the C3-substituted 1,3-bis(silyl)propenes, except for **2e**, were prepared from the corresponding 1,3-bis(silyl)propenes. *Typical experimental procedure for the preparation of **2b***: To a stirred solution of (*E*)-1,3-bis(trimethylsilyl)propene (560 mg, 3.0 mmol) in Et_2O (10 mL) were added TMEDA (450 μL, 3.0 mmol) and *n*-BuLi (1.6 mL, 2.5 M in hexanes) dropwise at −78 °C and the resultant mixture was stirred for 1 h before it was allowed to reach ambient temperature and left overnight. The reaction mixture was cooled to −78 °C, and MeI (210 μL, 3.3 mmol) was added. After 15 min, the solution was allowed to reach rt and stirred for an additional 1 h. The reaction was quenched by the addition of H_2O (5 mL). The aqueous phase was extracted (Et_2O, 3 × 10 mL), and the combined organic phases were washed (H_2O, 2 × 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane) to give **2b** (580 mg, 2.9 mmol) as a colorless oil in 97% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (dd, J = 18.7, 7.2 Hz, 1H), 5.40 (dd, J = 18.7, 1.4 Hz, 1H), 1.71–1.67 (m, 1H), 1.06 (d, J = 7.1 Hz, 3H), 0.04 (s, 9H), −0.04 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.0, 124.3, 30.6, 12.7, −0.9, −3.6. *For the preparation of the 1,3-bis(silyl)propenes see*: Knolker, H. J.; Foitzik, N.; Goesmann, H.; Graf, R.; Jones, P. G.; Wanzl, G. *Chem. Eur. J.* **1997**, *3*, 538–551. *Compound **2e** was prepared according to*: Despons, O.; Franzini, L.; Schlosser, M. *Synthesis* **1997**, 150–152.
9. *Typical experimental procedure for the preparation of **3***: To a stirred solution of silane **2a** (56 mg, 280 μmol), $BF_3 \cdot OEt_2$ (35 μL, 280 μmol) and 4 Å molecular sieves (100 mg/mL solvent) in CH_2Cl_2 (1 mL) at −78 °C was added a 0.01 M solution of aldehyde **1a** (29 mg, 140 μmol) and 1-methylnaphthalene (25 mg, 140 μmol) in CH_2Cl_2 (1 mL) dropwise over 1 h, and the resultant mixture was stirred overnight. The reaction was quenched by the addition of NH_4Cl (1 mL). The aqueous phase was extracted (CH_2Cl_2, 3 × 5 mL), and the combined organic phases were washed (H_2O, 2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane·CH_2Cl_2) to give **3a** (44 mg, 120 μmol) as a colorless oil in 86% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.33 (m, 4H), 7.29–7.26 (m, 1H), 4.51 (s, 2H), 3.90 (q, J = 6.5 Hz, 1H), 3.84–3.79 (m, 1H), 3.67–3.63 (m, 1H), 3.57–3.52 (m, 1H), 1.94 (dd, J = 13.4, 6.9 Hz, 2H), 1.27 (d, J = 5.9 Hz, 3H), 1.24–1.21 (m, 1H), 0.89 (dd, J = 8.4, 5.0 Hz, 1H), 0.05 (s, 9H), 0.02 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 138.6, 128.3, 127.7, 127.5, 79.4, 76.8, 73.1, 69.0, 34.9, 33.9, 33.6, 22.3, −0.6, −2.4.
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